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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/997,464	12/23/97	STERN	D 54202/JPW/SB

EXAMINER	
KERR, I	
ART UNIT	**PAPER NUMBER**
1633	7

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DATE MAILED: 04/13/99

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/997,464	Applicant(s) Stern et al.
	Examiner Janet M. Kerr	Group Art Unit 1633

☒ Responsive t communication(s) filed on *Apr 5, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-33* is/are pending in the application.

Of the above, claim(s) *6-10 and 13-33* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5, 11, and 12* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

The Information Disclosure Statement, filed on 11/12/98, has been entered.

Applicants' election, with traverse, of Group I, claims 1-5, 11, and 12, in response to the restriction requirement, filed on 4/5/99, has been entered.

Claims 1-32 are pending.

Claims 1-5, 11 and 12 are being examined on the merits for the reasons set forth below.

Applicant's arguments filed 4/5/99 have been fully considered but they are not persuasive.

Applicants argue that the restriction requirement is improper because the claimed invention is related as the claims all involve compounds which inhibit neurotoxicity. In this regard, Applicants argue that the restriction is improper as the inventions are not both independent and distinct as required in 35 U.S.C. 121. Moreover, Applicants assert that search and consideration of the claimed invention would not be a serious burden because a search of the prior art for subject matter defined by the claims in any of Groups I-V would necessarily overlap and possibly identify art pertaining to the subject matter defined by claims in any of the other groups. Applicants indicate, as an example, that Groups I, II, and V would be searched under class 435, therefore it would not be a serious burden to examine Groups I, II, and V together.

While the invention involves compounds which inhibit neurotoxicity, the claims are not drawn to the compounds per se. Using the example provided by Applicants, the invention is directed to methods of screening and cells which have been modified by introduction of recombinant DNA into the cells. The claims of Group I are directed to a method for evaluating the ability of a compound to inhibit neurotoxicity which requires cells containing RAGE and a mutant presenilin-2 protein, and a step of measuring cell death. The claims of Group II, directed to a method for evaluating the ability of a compound to inhibit binding of amyloid β peptide to a receptor, requires cells containing RAGE and a mutant presenelin-2, and a step of measuring receptor-ligand binding activity. While the methods require the same cells, the measurements used for evaluating the compounds which are added to the cells are distinct. Moreover, since the

measurement step required in the method of Group I, determination of cell death, is not required to reduce to practice the method of Group II, and the measurement step of Group II, determination of receptor-ligand binding, is not required to reduce to practice the method of Group I, the methods are also distinct.

With regard to the cells required for the methods of Groups I and II, and the claimed cells of Group V, it should be noted that the cells of Groups I and II are not required to be modified using recombinant DNA technology as these cells can be obtained from naturally occurring sources. The cells of Group V, however, require introduction of foreign DNA for expression of the mutant protein. Thus, the sources of the cells and/or the methods of obtaining the cells are distinct as they require different technical considerations. Moreover, the recombinant cells of Group V are not required to reduce to practice the methods of Groups I and II, nor are the methods of Groups I and II required to reduce to practice the composition of Group V.

With regard to search and consideration of the claimed invention, following the example provided by Applicants, it should be noted that a reference which would anticipate the invention of Group I, which requires the step of measuring cell death, would not necessarily anticipate or even make obvious the step of measuring receptor-ligand binding activity. Moreover, a reference for a composition comprising transformed cells would not necessarily anticipate or make obvious the methods of Groups I and II.

For the reasons of record and the reasons discussed above, the restriction requirement is maintained.

The abstract of the disclosure is objected to because of it contains multiple paragraphs and exceeds 250 words in length. Correction is required. See MPEP § 608.01(b).

Claims 1-5, 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite by the phrase "mutant presenilin-2 protein" because it is unclear what type of mutation is required in the protein for the cell to be suitable in the claimed method.

Claim 2 is rendered vague and indefinite by the phrase "tumor cell" because it is unclear which type of tumor is suitable in the claimed method.

Claim 3 is rendered vague and indefinite by the term "polymer" as it is unclear what type of polymer is encompassed in the claim, e.g., is the polymer a synthetic polymer, a naturally occurring polymer, a nucleic acid polymer, a carbohydrate polymer?

Claim 3 is further rendered vague and indefinite by the phrase "small molecule" because it is unclear what Applicants intend as "small", i.e., does the term small denote a weight limitation or a spatial limitation on the molecule?

Claim 5 is rendered vague and indefinite by the phrase "mutant presenilin-2 is overexpressed" because it is unclear if the overexpression occurs at the transcriptional or translational level. The phrase as written, lacks proper antecedent basis. Applicants should insert the term "protein" after "mutant presenilin-2".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 11, and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to a method for evaluating the ability of a compound to inhibit neurotoxicity. The method requires a cell which expresses a receptor for advanced glycation end product protein and a mutant presenilin-2 protein. However, the specification fails to provide an enabling disclosure as to the publicly availability of the cell a mutant presenilin-2 protein, or how to make the cell such that the mutant presenilin-2 protein is expressed.

The specification teaches numerous cell types which can be used in the method, but does not disclose if these cells contain a naturally-occurring mutation in the presenilin-2 protein, or whether genetic modification of the cell types is required. With regard to the type of mutation, the specification teaches that the mutant protein may be a result of a deletion, substitution, insertion, or point mutation. Moreover, the protein can be of human or non-human origin, and can be overexpressed. However, the specification fails to proved an enabling disclosure for how to make generate these various mutations as there is no teaching as to specific presenilin-2 sequences and/or restriction maps to generate constructs for transfection of the cells such that they express or over-express the mutant presenilin-2 protein.

While the specification discloses, by reference to a printed publication, that PC12 cells are transfected with a mutant presenilin-2 construct, the specification does not disclose how to make the construct for transfecting the cells. The attempt to incorporate subject matter into this application by reference to Wolozin (1996) is improper because a cell containing the mutant presenilin-2 protein is a critical feature of the invention.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In view of the non-enabling disclosure for making a cell which expresses or over-expresses a mutant presenilin-2 protein, the method of using the cell, and the product identified by the method are also not enabled.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Bartus *et al.* (U.S. Patent No. 5,444,042, 1995).

The claimed invention is drawn to a method of evaluating the ability of a compound to inhibit neurotoxicity and compounds identified by the method, i.e., product-by-process claims. Although the claims are non-enabled for the claim-designated cells used in the assay, the method for measuring the extent of cell death upon administration of a compound is known in the art.

Bartus *et al.* disclose that calpain activation is an event central to many cases of brain atrophy and degeneration and that inhibition of calpain alone is sufficient to inhibit or prevent cell deterioration and loss (see column 6, lines 16-23). Bartus *et al.* teach a method of evaluating the ability of a compound to inhibit neurotoxicity comprising treating N18-RE-105 cells with calpain inhibitors and measuring the extent of cell death. The calpain inhibitors effectively block cell death in an *in vitro* model for neuropathology (see column 73, lines 5-24). The compounds can be formulated as pharmaceutical compositions comprising the compound of interest in a pharmaceutically acceptable formulation containing a carrier material (see column 4, lines 48-54 and column 66, lines 36-40).

Thus, the method and the products identified by the method are anticipated by Bartus *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 11, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bartus *et al.*

The claimed invention is drawn to a method of evaluating the ability of a compound to inhibit neurotoxicity and compounds identified by the method. Although the claims are non-enabled for the claim-designated cells used in the assay, the method for measuring the extent of cell death upon administration of a compound is known in the art.

Bartus *et al.* disclose that calpain activation is an event central to many cases of brain atrophy and degeneration and that inhibition of calpain alone is sufficient to inhibit or prevent cell deterioration and loss (see column 6, lines 16-23). Bartus *et al.* teach a method of evaluating the ability of compound to inhibit neurotoxicity comprising treating N18-RE-105 cells with calpain inhibitors and measuring the extent of cell death. The calpain inhibitors effectively block cell death in an *in vitro* model for neuropathology (see column 73, lines 5-24).

Bartus *et al.* do not disclose all of the claim-designated compounds recited in claim 3. However, as the method of evaluating compounds is known in the art, it would have been obvious

and well within the purview of one of ordinary skill in the art to substitute different classes of compounds in various formulations in the method of evaluating the effect of these compounds on cell death absent evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Brian Stanton, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-2801. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600
April 12, 1999

BRIAN R. STANTON, PH.D
PRIMARY EXAMINER